



IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of : Confirmation No. 1112
Edwin SOUTHERN : Attorney Docket No. 2004_0200
Serial No. 10/772,467 : Group Art Unit 1631
Filed February 6, 2004 : Examiner Anna Skibinsky
ANALYZING POLYNUCLEOTIDE SEQUENCES : Mail Stop: AF

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ACCOUNT NO 23-0975

PRE-APPEAL BRIEF REQUEST FOR REVIEW

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The claims under consideration are 17-27, 86 and 87, filed 29 May 2007. All of these claims have been rejected under 103(a) as being unpatentable over Stavrianopoulos (US-4,994,373) in view of Matkovich (US-4,828,386). The applicant is requesting a review of the 103(a) rejections in the Final Office Action of 23 August 2007, as supplemented by the Advisory Action of 21 December 2007. A Notice of Appeal and PTO fee are filed concurrently herewith.

Claim 17

The examiner sees in Stavrianopoulos an apparatus in which multiple DNA samples are attached to separate depressions/wells on an impermeable surface of a solid support in a format suitable for hybridisation. Claim 17 differs from this disclosure by at least the feature that the claimed apparatus includes "porous material attached to the impermeable surface". The examiner finds this extra feature in Matkovich.

The applicant does not believe that a skilled person would obviously combine Stavrianopoulos and Matkovich. Stavrianopoulos deals with nucleic acid assays, whereas Matkovich is explicitly concerned with antibody assays (*e.g.* see the *Background* section therein,

culminating with the statement: “Accordingly, there remains a need for improvements in multiwell plates to provide for increased antibody binding in a more reliable manner”. In addition, the *Summary of the Invention* section refers specifically to surfaces “capable of binding antibody”, etc.). A skilled person starting with the DNA assay of Stavrianopoulos would not obviously have looked to the teachings of Matkovich because it is from a different technical field (antibodies vs. nucleic acids); rather, they would have looked within their own field (nucleic acid assays).

Moreover, a skilled reader of Stavrianopoulos would not have modified the apparatus by introducing a porous material for nucleic acid attachment because Stavrianopoulos had already considered the use of such materials and had discarded them. At column 5, lines 46-52, Stavrianopoulos concludes that porous support materials are “less desirable for practice of the method of the present invention”. It is not reasonable to give the skilled person a desire to ignore the intrinsic teaching of their starting point. Stavrianopoulos is teaching away from the attachment of nucleic acids to porous materials, and so is teaching away from the claimed apparatus and from the modifications disclosed in Matkovich.

The examiner’s rejection of claim 17 requires a skilled person starting with Stavrianopoulos to look to an unrelated technical field for a disclosure that contradicts the clear preferences of Stavrianopoulos. A person of ordinary skill would not have made these choices, and it is only with hindsight that they seem reasonable (*KSR v. Teleflex*: “A factfinder should be aware, of course, of the distortion caused by hindsight bias and must be cautious of arguments reliant upon ex post reasoning”).

Claim 23

Claim 23 differs from claim 17 by requiring the oligonucleotides to be “covalently attached to the porous material”.

In the Final Office Action the examiner stated that Stavrianopoulos discloses covalent attachment of the DNA samples to the impermeable surface. Although the word “covalent” is frequently used in Stavrianopoulos, this is exclusively in the context of the linkage of a nucleic acid to a chemical label, not in the context of the linkage of a nucleic acid to the solid support. Nor is covalent attachment an inherent property of the Stavrianopoulos devices. Technical

arguments in support of this position can be found in the applicant's submissions of 20th November 2007 (pages 9-10) and the supplemental response of 14th December 2007. These technical arguments seem to have been accepted in the Advisory Action, but for teaching of covalent attachment the examiner instead cites the disclosure at the end of column 4 in Matkovich.

The applicant does not believe that a skilled person who combined Stavrianopoulos and Matkovich (itself an unreasonable combination; see above) would then select covalent attachment from the possibilities given in Matkovich. The end of column 4 states that reactants can have different natures ("ionic, molecular or macromolecular") and then states that various possible attachment techniques can be used ("... by strong physical forces or by being bonded in some manner, such as covalent chemical coupling ..."). The examiner has selected one of these in particular from Matkovich, but has not given any justification for making this selection in particular. As explained in the applicant's November and December submissions, Stavrianopoulos was evidently aiming for a charged surface so as to facilitate non-covalent retention of DNA, which is a poly-anionic substance. The examiner has given no reasonable justification why a skilled person who looked to Matkovich would reject Stavrianopoulos's choice of charged surfaces for "fixing any negatively charged polyelectrolytes applied thereto" (Stavrianopoulos, column 8, lines 32-35) and choose instead to use covalent bonding. Again the rejection suffers from "the distortion caused by hindsight" because a reasonable skilled person would not arbitrarily select covalent attachment chemistry for an analyte that is intrinsically ionic in nature and that had been deliberately immobilised non-covalently in the examiner's starting point.

Claim 24

Claim 24 differs from claim 23 by additionally specifying that the covalent attachment is "by a terminal nucleotide".

In the Final Office Action the examiner asserted that the attachment chemistry in Stavrianopoulos used "covalent attachment ... which involves the binding with terminal nucleotide". As mentioned above, covalent attachment is neither an explicit nor implicit aspect of the attachment chemistry in Stavrianopoulos. This point seems to have been conceded in the

Advisory Action, but the examiner turns instead to Matkovich for the teaching of covalent attachment (see above). Even if the skilled person had combined Stavrianopoulos and Matkovich, and had then selected covalent attachment from Matkovich's teaching (all of which is denied), the examiner has not built even a *prima facie* case for obviousness of attachment "by a terminal nucleotide".

Covalent attachment of nucleic acids to solid supports does not inevitably occur through a terminal nucleotide. On the contrary, it is known that nucleic acids can attach to porous nylon membranes by cross-linking between thymine residues and surface amine groups. Moreover, a standard way of ensuring covalent binding of nucleic acids to a nylon membrane is to use UV irradiation which, again, causes thymine residues (and to a lesser extent other nucleotides) to react with amine groups on the membrane. Such thymine residues are present along the length of a nucleic acid, and so standard covalent attachment of nucleic acids to porous membranes is specifically not "by a terminal nucleotide". Indeed, UV-induced attachment can occur at multiple sites along a nucleotide, such that over-irradiation can destroy the ability of a nucleic acid to hybridise to targets.

Moreover, subsequent to the present invention, covalent attachment via a terminal nucleotide has been acknowledged in the art as desirable for nucleic acid arrays. The applicant previously referred to Dawson *et al.*, where in 2005 the author wrote: "... a single terminal covalent attachment is preferred for short oligonucleotides. This terminal covalent attachment allows the entire oligonucleotide to be available for hybridization and to withstand the high temperatures and salt concentrations often required during the stringent washing conditions in subsequent steps of microarray processing."

These advantages flow directly from the array synthesis methods used in the present application; they are not a feature of the attachments taught by either Stavrianopoulos or Matkovich.

Thus, in addition to claims 17 and 23, the applicant requests specific reconsideration of the rejection against claim 24. The examiner has not given a reasonable *prima facie* rejection of claim 24 and, moreover, the specific advantages of these claimed arrays have been acknowledged in the art.

Further points

The above points are the main issues requested for panel review. In addition, however, the applicant maintains its position in relation to previous objections that have been raised. For example, the applicant believes that the immobilised nucleic acids in Stavrianopoulos are not "oligonucleotides with predetermined sequences", and that the different wells disclosed in Stavrianopoulos are separate surfaces, not a single surface. The main reasons for the request for panel review, though, are the rejections of claims 24, 23 and 17.

Respectfully submitted,

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